Reviewer: Rick J. Whiting **Date: February 15, 2011**
Risk Manager (EPA): 23

STUDY TYPE: Acute Oral Toxicity - Rat; OCSPP 870.1100; OECD 425

TEST MATERIAL: GF-2633 (Triisopropanolamine salt of Aminopyralid – 8.28 wt%; 2,4-D, dimethylamine salt – 42.2 wt%; Lot No. F1506-50, TSN032903-0001; pH: 7-8; soluble in water; clear liquid)

CITATION: Durando, J. (2010) GF-2633: Acute Oral Toxicity Up and Down Procedure in Rats. Project Number: 101013, 29302. Unpublished study prepared by Eurofins/Product Safety Laboratories. 31 p. July 1, 2010. MRID 48173003

SPONSOR: The Dow Chemical Company, Midland, MI 48674

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 48173003), young adult female Fischer 344 rats (age: 9-10 weeks; weight: 128-145 g; source: Harlan, Indianapolis, IN) were given a single oral dose of GF-2633 (Triisopropanolamine salt of Aminopyralid – 8.28 wt%; 2,4-D, dimethylamine salt – 42.2 wt%; Lot No. F1506-50, TSN032903-0001; pH: 7-8; soluble in water; clear liquid). The test material was administered as received. Based on an estimate of the LD_{50} supplied by the Sponsor (1,800 mg/kg and an assumed sigma of 0.2), a Main Test was conducted using a default starting dose level of 1,140 mg/kg which was administered to one healthy female rat by oral gavage. Following the Up and Down procedure, six additional animals were dosed at levels of 1,140 or 2,000 mg/kg. Females were selected for the test because they are frequently more sensitive to the toxicity of test compounds than males.

All animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for up to 14 days after dosing or until death occurred. Body weights were recorded prior to administration and again on Days 7 and 14 (study termination) following dosing or after death. Necropsies were performed on all animals at terminal sacrifice.

Results from page 11 of the study:

1,140 mg/kg Dose level (2 animals): Both animals survived test substance administration and gained body weight during the study. Following administration, one animal was hypoactive and exhibited ano-genital staining, but it recovered by Day 3 and along with the other animal appeared active and healthy for the remainder of the 14-day observation period. No gross abnormalities were noted for these animals when necropsied at the conclusion of the 14-day observation period.

2,000 mg/kg Dose level (5 animals): One animal died within 2 days of test substance administration. Prior to death, this animal was hypoactive, exhibited reduced fecal volume and prone posture. Following administration, the surviving animals were hypoactive and/or exhibited reduced fecal volume. However, they recovered by Day 2, gained body weight and appeared active and healthy for the remainder 14-day observation period. Gross necropsy of the decedent revealed red intestines. No gross abnormalities were noted for any of the euthanized animals when necropsied at the conclusion of the 14-day observation period.

Oral LD_{50} Females = 2000 mg/kg bw

Based on the Oral LD_{50} in females, GF-2633 is classified as EPA Toxicity Category III.

This acute oral study is classified as Acceptable. It does satisfy the guideline requirement for an acute oral study (OCSPP 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Individual animals were dosed as follows:

Main Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	3101	1140	S	S
2	3102	2000	S	S
3	3103	2000	D	D
4	3104	1140	S	S
5	3105	2000	S	S
6	3106	2000	S	S
7	3107	2000	S	S

S = survival D = death

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Test/Substance: GF-2633
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): 1800
Assumed sigma (mg/kg): 0.2

Recommended dose progression: 2000, 1140, 720, 450, 290, 180, 114, 72, 45, 29, 18, 11.4, 7.2, 4.5, 2.9, 1.8

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	3101	1140	O	O
2	3102	2000	O	O
3	3103	2000	X	X
4	3104	1140	O	O
5	3105	2000	O	O
6	3106	2000	O	O
7	3107	2000	O	O

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 3 at Limit Dose.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
1140	2	0	2
2000	4	1	5
All Doses	6	1	7

Statistical Estimate based on long term outcomes:

Estimated LD50 = 2000 (The one dose with partial response. 95% PL Confidence interval is 1804 to Greater than 20,0001).

Statistics: Acute Oral Toxicity (Guideline 425) Statistical Program (Westat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or LD_{50} and confidence limit calculations.

A. Mortality: One animal receiving 2000 mg/kg died within 2 days of test material administration.

B. Body weights: All surviving animals gained body weight during the study.

C. Clinical observations:

1,140 mg/kg Dose level (2 animals): Following administration, one animal was hypoactive and exhibited ano-genital staining, but it recovered by Day 3 and along with the other animal appeared active and healthy for the remainder of the 14-day observation period.

2,000 mg/kg Dose level (5 animals): One animal died within 2 days of test substance administration. Prior to death, this animal was hypoactive, exhibited reduced fecal volume and prone posture. Following administration, the surviving animals were hypoactive and/or exhibited reduced fecal volume. However, they recovered by Day 2 and appeared active and healthy for the remainder 14-day observation period.

D. Gross Necropsy:

1,140 mg/kg Dose level (2 animals): No gross abnormalities were noted for these animals when necropsied at the conclusion of the 14-day observation period.

2,000 mg/kg Dose level (5 animals): Gross necropsy of the decedent revealed red intestines. No gross abnormalities were noted for any of the euthanized animals when necropsied at the conclusion of the 14-day observation period

E. Reviewer's Conclusions: TRB agrees with the study author regarding the acute oral LD_{50}. GF-2633 is classified as EPA Toxicity Category III.

F. Deficiencies: None.